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08/791,240 01/30/97 RYNCARZ

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[REDACTED] EXAMINER

HM22/0318

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ART UNIT [REDACTED] PAPER NUMBER

1634
DATE MAILED:

24

03/18/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/791,240

Applicant(s)

Alexander J. Ryncarz

Examiner

Bradley L. Sisson

Group Art Unit

1634

 Responsive to communication(s) filed on 10/27/98, 12/4/98, and 1/13/99. This action is **FINAL**. Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims Claim(s) 1-58 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

 Claim(s) _____ is/are allowed. Claim(s) 1-58 is/are rejected. Claim(s) _____ is/are objected to. Claims _____ are subject to restriction or election requirement.**Application Papers** See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. The drawing(s) filed on _____ is/are objected to by the Examiner. The proposed drawing correction, filed on _____ is approved disapproved. The specification is objected to by the Examiner. The oath or declaration is objected to by the Examiner.**Priority under 35 U.S.C. § 119** Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d). All Some* None of the CERTIFIED copies of the priority documents have been received. received in Application No. (Series Code/Serial Number) _____. received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

 Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).**Attachment(s)** Notice of References Cited, PTO-892 Information Disclosure Statement(s), PTO-1449, Paper No(s). 22 Interview Summary, PTO-413 Notice of Draftsperson's Patent Drawing Review, PTO-948 Notice of Informal Patent Application, PTO-152**... SEE OFFICE ACTION ON THE FOLLOWING PAGES ...**

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DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7 December 1998 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/791,240 is acceptable and a CPA has been established. An action on the CPA follows.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

3. The disclosure is objected to because of the following informalities: Pages 9, 10, 51, and 68 recite the serial number of several US patent applications; however, the status of these applications is not indicated. In some instances the cases recited have been abandoned in favor of a file-wrapper-continuation application. In such instances, it is suggested that the new serial number be provided and the current status of the continuation application be provided. In other

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instances reference has been made to applications which have either been allowed or have become abandoned. While one may incorporate essential subject matter by reference to an issued US patent, such is not permitted with respect to a US patent application that is abandoned. Should any of the abandoned applications contain essential subject matter, applicant is urged to provide an amendment to the specification which brings that essential subject matter into the specification of the captioned application.

Appropriate correction is required.

4. The use of the trademark TRITON X-100 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-58 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The conditions and characteristics of the starting material are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the

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disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). While claims 1, 2, 9, 25, 39, and 58 are each drawn to a related method, claim 1 is cited to exemplify the issue at hand. Claim 1, in *Jepson* format, states that the improvement comprises:

forming said extension products in the presence of a second polynucleotide, to which said oligonucleotide primer hybridizes except for the 3'-end of said oligonucleotide primer, under conditions wherein the extension of said oligonucleotide primer along said second polynucleotide is controlled relative to the extension of said oligonucleotide primer along said target sequence (emphasis added).

7. In order to achieve the requisite annealing/hybridization conditions whereby one does not have the 3'-end of the primer anneal to the second nucleic acid, it is imperative that the reaction mixture be accurately manipulated. As presently worded, the nucleotides of the second polynucleotide may have the same nucleotide residue sequence in that region corresponding to the primer annealing site. The claim is silent as to just how one would effect such annealing results and, by extension, the appropriate level of control, regardless of the similarity at the 3'-end of the primer to the second polynucleotide. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.
2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

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3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25° - 30° C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

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Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

As set forth in independent claims 2, 9, 25, 39, 58, there are multiple primers and in at least claim 58 the first and second primers can be the same or different. Like the situation in claim 1, there is to employed improved conditions that permit the controlled extension of the first oligonucleotide primer along a second polynucleotide relative to the extension of the first primer to the target sequence. If the first and second primers are the same, then there is but one type of primer and the conditions that are required would correspond to the issues set forth for claim 1. If, however, there is a second and a first primer and they are different and they each are directed to different target polynucleotides, then it is unclear what conditions for hybridization and selective annealing would need to be employed so to achieve the requisite end product(s).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-58 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the conditions and how they are manipulated so to achieve the

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requisite and improved level of control. The claims set forth what the intended end-product is to be and what the conditions are to yield, however, the conditions under which the various embodiments are to be practiced and the steps practiced in relation to these conditions, are essential to the claimed method.

Conclusion

10. No claim is allowed.
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978 and whose e-mail address is bradley.sisson@uspto.gov. The examiner can normally be reached on Monday through Thursday from 6:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone numbers for Group 1630 are (703) 305-3014 and (703) 305-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist for Technology Center 1600 whose telephone number is (703) 308-0196.

B. L. Sisson
BRADLEY L. SISSON
PRIMARY EXAMINER
GROUP 1600 1634
3-13-99